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EXHIBIT

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The National Human Genome Research Institute

Results From First Human Gene Therapy Clinical Trial

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Two years after receiving their last infusions of genetically altered cells to boost their weakened immune systems, the first patients ever to undergo gene therapy are still healthy and benefiting from the treatment.

According to a historic research paper published today in Science, the two girls still have white blood cells bearing copies of the replacement ADA gene. Patient 1, whose health improved significantly following gene therapy, has maintained a normal white blood cell count as well as measurable levels of the ADA enzyme, which was almost nonexistent prior to the treatment. Both girls also have developed stronger immune systems, showing improved immune reactions in a battery of tests conducted over the course of the four-year study.

These results indicate replacement genes can be expressed stably in white blood cells over long periods of time. They also demonstrate that the disabled virus used to transfer the replacement gene into the cell, called a viral vector, will not cause adverse, short-term health effects. Both issues are considered critical in establishing the safety and efficacy of gene therapy.

But, the 19 authors of the paper hastened to add that, as a preliminary investigation into the safety and effectiveness of gene therapy, several aspects of gene therapy remain to be perfected. One of these is more consistent methods of transporting a gene into a cell using a type of virus called a retrovirus. Although the gene-bearing retrovirus readily integrated into the white blood cells of Patient 1, the process was less efficient in Patient 2. Only about 1 percent of her T cells incorporated the virus into their DNA.

Based on the results of this landmark study, the authors concluded that with further refinement, "gene therapy can be a safe and effective addition to treatment" for some people born with severe combined immunodeficiency disease (SCID). Affecting one out of every 150,000 live births, SCID is one of a group of about 80 rare genetic disorders involving the body's immune system.

"The results of the study are very gratifying and will help to forward the field of gene therapy," said R. Michael Blaese, M.D., lead author and scientist now with the National Human Genome Research Institute. "But, as a physician, I'm

most pleased that the girls are doing so well four years later. It's really been remarkable to observe."

If most diseases can be traced to an alteration in a gene, then gene therapy represents the ultimate medical cure. It attempts to eradicate disease by healing the gene itself. Gene therapy does this by inserting a functioning copy of the gene into DNA and augmenting the cell's production of the lacking protein.

While experiments in gene therapy have potentially enormous medical implications, scientists face numerous technical hurdles in perfecting the treatment. These include developing effective gene-transfer strategies, tailoring them to the dynamics of various cells and tissues, maintaining long-term cell survival, and establishing reliable gene expression. To evaluate the future prospects of safe and effective gene therapy, the NIH is currently reviewing the state of the science.

In 1990, on the heels of successful feasibility studies on gene therapy, a team of scientists at the National Institutes of Health received approval from the agency's Recombinant DNA Advisory Committee, which oversees gene therapy protocols in the United States, to proceed with the first clinical trial to evaluate the procedure in people. By the spring of 1990, the researchers had identified two unrelated girls, ages 4 and 9, to participate in the study. Both were born with an extremely rare condition called adenosine deaminase (ADA) deficiency, a form of SCID.

Those who inherit ADA deficiency have extremely low levels of specialized white blood cells, called T cells, to orchestrate the immune system's attack on invading organisms. With a severely weakened immune system, people with ADA deficiency are susceptible to chronic and repeated infections. In most cases, one of these infections will prove fatal during childhood.

ADA deficiency is a genetic disease. Affected children are born with alterations, or misspellings, in both copies of their ADA gene. This sets off a metabolic "domino effect." The altered genes produce non-functional copies of the enzyme ADA, preventing a crucial chemical reaction mediated by the enzyme from being carried out. Ultimately, aberrant chemicals build up in the blood that prove lethal to circulating T cells.

For those who have a genetically compatible family member, a bone marrow transplant can introduce viable T cells into their bodies, reconstituting the immune system and in some cases curing the disease. But for those who don't have a matching donor, the next best option is enzyme replacement therapy, in which a synthetic version of the ADA enzyme is injected into patients to help more T cells survive. While this treatment, called PEG-ADA, has improved the well-being and immune function of most ADA patients, it does not cure them of the disease. After initial improvement, many patients tend to have a gradual decline in their number of immune cells.

With PEG-ADA serving as a therapeutic safety net for the girls, the NIH researchers initiated gene therapy on September 14, 1990 for Patient 1 and on

January 31, 1991 for Patient 2. The researchers drew blood from the girls and induced the T cells from the blood to replicate in culture. The next step was to transfer ADA-bearing retroviral vectors into the cultured T cells. Allowing enough time for the vector to integrate into the DNA and transfer the gene, the scientists reinfused the enhanced T cells back intothe girls about 12 days after drawing the blood and waited for expression of the replacement gene. Patient 1 received 11 infusions over approximately two years, and Patient 2 had 12 infusions during 18 months.

The results of gene therapy were remarkable in both girls. Patient 1, who had spent much of her life isolated in her home as a protection against possible infections, had her T-cell count rise within the first six months to normal levels. By the two-year mark, she also had logged a steady increase in functioning ADA enzyme, nearing half the level of her parents. With her health much improved, Patient 1 began to attend school regularly and lead a relatively normal childhood.

In Patient 2, the short-term results also were striking. Although the NIH scientists succeeded at inserting the ADA-bearing vector into only about 1 percent of her T cells, Patient 2 had a rapid rise in her T cell count and showed an improved response in immune function tests. Her lymph nodes and tonsils, where developing immune cells reside, grew larger also suggesting increased immune activity.

Despite the impressive early results, many wondered whether the findings would hold up after the girls stopped receiving treatment. Would the T cells simply die off after a few weeks, causing T cell and ADA enzyme levels to plummet?

Today's paper offers the first follow-up data to help answer this question. It shows that increased levels of T cells and active ADA enzyme can be sustained long after gene therapy has ceased. In Patient 1, the researchers said they continue to find evidence of the integrated vector. In fact, a blood sample tested approximately two years after her last infusion showed the vector present in nearly 100 percent of her T cells. In Patient 2, copies of the vector were detected well over a year after the conclusion of gene therapy.

The scientists report that not only are the vectors still present, but the girls continue to have improved immune function. Both patients now have immune systems that respond to a wide array of antigens.

For instance, prior to undergoing gene therapy, Patient 2 had no positive T cell skin tests. But since participating in the study, her immune system has responded normally during these tests, including testing conducted almost a year-and-a-half after her final infusion. She also suffered previously from chronic headaches and sinus infections. Both problems have now ceased.

Although the girls today have stronger immune systems than five years ago when they had been treated with only PEG-ADA, the researchers still don't have a complete picture of the contribution of each treatment in improving the

girls' immune function. Both patients have reduced their dosage of PEG-ADA by half and still maintain good immune function. By contrast, when ADA patients treated with PEG-ADA alone have reduced their dosage of the enzyme, their immune function has usually worsened.

While withdrawing the PEG-ADA would be the next step in evaluating the outcome of gene therapy in this study, the scientists say they are unsure of how it would affect the girls. "As a scientist, I would very much like to know the answer to this question," said Dr. Blaese. "But as their pediatrician, I'm not yet prepared to take the step of completely stopping their enzyme treatment and possibly putting them at risk until we know even more about the extent and duration of their improved immune function."

This landmark clinical trial involved an unprecedented collaboration of scientists and research institutions. These include Dr. W. French Anderson, formerly of NIH's National Heart, Lung, and Blood Institute and now with the Norris Cancer Center at the University of Southern California School of Medicine; Drs. Kenneth Culver, Mario Clerici, Gene Shearer, Jay Greenblatt, and Steven Rosenberg of the NIH's National Cancer Institute; Drs. Charles Carter, Thomas Fleisher, and Harvey Klein of NIH's Warren Grant Magnuson Clinical Center; Dr. Dusty Miller of the Fred Hutchinson Cancer Center at the University of Washington; Dr. Melvin Berger of Case Western Reserve University School of Medicine; Drs. Yawen Chiang and Paul Tolstochev of Genetic Therapy, Inc.; and Drs. R. Michael Blaese, W. Jay Ramsey, Linda Muul, and Richard A. Morgan, now with the NIH's National Center for Human Genome Research.

The National Human Genome Research Institute, part of the National Institutes of Health, oversees NIH's role in the Human Genome Project, an international research effort to develop tools for gene discovery and analysis, and applies these technologies to the study of human genetic disease.

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